Istituto Superiore di Sanità

Strumenti per la sorveglianza e la presa in carico delle persone con autismo:

il ruolo dei pediatri nel riconoscimento dei bambini a rischio nei primi 24 mesi di vita

22-23 Ottobre 2015

Dipartimento di Biologia Cellulare e Neuroscienze
in collaborazione con
ACP-Associazione Culturale pediatri
CROME-LIFE-Cross-Mediterranean Environment and Health Network

Direttore del corso:

A. Venerosi
Dipartimento Biologia cellulare e neuroscienze
Istituto Superiore di Sanità, Roma
(tel. 06 49903502, e-mail: venerosi@iss.it)

Segreteria Scientifica

M.L. Scattoni
Dipartimento Biologia cellulare e neuroscienze
Istituto Superiore di Sanità, Roma
(tel. 06 49903104, e-mail: marialuisa.scattoni@iss.it)

F. Chiarotti
Dipartimento Biologia cellulare e neuroscienze
Istituto Superiore di Sanità, Roma
(tel. 06 49902447, e-mail: flavia.chiarotti@iss.it)

M. Soldateschi
Asl 5 Pisa, Associazione Culturale Pediatri
(e-mail: massimo.soldateschi@alice.it)

Segreteria Tecnica

(FAX: +39-06-4957821)

L. Felici, Servizio Informatico, Documentazione, Biblioteca, Attività Editoriale
Istituto Superiore di Sanità, Roma
(06 4990 2520, e-mail: luca.felici@iss.it)

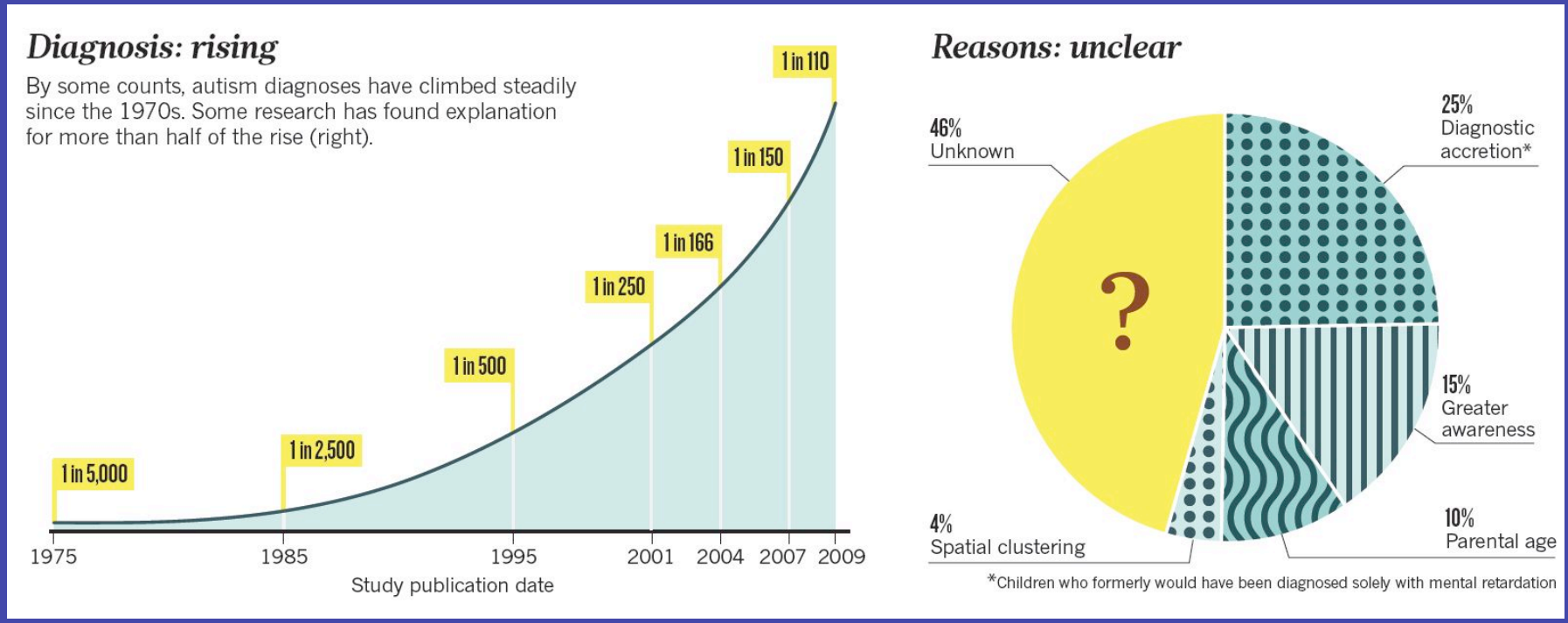
E. Gambini, Servizio Informatico, Documentazione, Biblioteca, Attività Editoriale
Istituto Superiore di Sanità, Roma
(06 4990 2426, e-mail: elisabetta.gambini@iss.it)

V. Ambrosio
Dipartimento Biologia cellulare e neuroscienze
Istituto Superiore di Sanità, Roma
(06 4990 2447, e-mail: valentina84@yahoo.com)

INFORMAZIONI GENERALI

Sede: Istituto Superiore di Sanità, Aula Marotta.
Ingresso: Viale Castro Laurenziano, n° 10

PREVALENZA


Diagnosis: rising
By some counts, autism diagnoses have climbed steadily since the 1970s. Some research has found explanation for more than half of the rise (right).
1 in 5,000
1 in 2,500
1 in 500
1 in 250
1 in 166
1 in 150
1 in 110
1975
1985
1995
2001
2004
2007
2009
Study publication date
Reasons: unclear
46% Unknown
25% Diagnostic accretion*
15% Greater awareness
10% Parental age
4% Spatial clustering
?
*Children who formerly would have been diagnosed solely with mental retardation

Geni e ambiente

COMPONENTE AMBIENTALE | **DISTURBI DELLO SPETTRO AUTISTICO** | **COMPONENTE GENETICA**

Fattori Prenatali

- **Virus della rosolia**
- **Elevati livelli di testosterone**
- **Sostanze che causano difetti alla nascita: alcool etilico, acido valproico** (farmaco antiepilettico)**, talidomide** (farmaco tranquillante ed antiemetico)
- **Sono in studio gli organofosfati** (sostanze comunemente usate come pesticidi in agricoltura e come insetticidi in ambito domestico)
- **Età dei genitori (Idring et al. International Journal of Epidemiology, 2014 Sandin et al. Molecular Psychiatry 2015)**

Fattori Perinatali

- **Peso alla nascita, SGA**
- **Apgar score**
- **Distress fetale al parto**
- **Infezioni perinatali (neuroinfiammazione?)**
- **Distanza tra le nascite (< 1 anno)**
- **Sostanze neurotossiche (mercurio, 'inquinamento atmosferico', pesticidi)**

MICROARRAY

Copy number variations (CNVs) (Delezione o duplicazione di piccoli segmenti di DNA)

Mutazioni puntiformi (SNPs) (Polimorfismo di un singolo nucleotide)

Rodgers et al (2015). Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress, *PNAS, 1-6*.

www.pnas.org/cgi/doi/10.1073/pnas.1508347112

Proceedings of the National Academy of Sciences
www.pnas.org
(/) > Early Edition (/content/early/recent) > Ali B. Rodgers, doi: 10.1073/pnas.1508347112

Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress

Ali B. Rodgers (/search?author1=Ali+B.+Rodgers&sortspec=date&submit=Submit), Christopher P. Morgan (/search?author1=Christopher+P.+Morgan&sortspec=date&submit=Submit), N. Adrian Leu (/search?author1=N.+Adrian+Leu&sortspec=date&submit=Submit), and Tracy L. Bale (/search?author1=Tracy+L.+Bale&sortspec=date&submit=Submit)[1]

Author Affiliations

Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved September 11, 2015 (received for review April 28, 2015)

Abstract | Authors & Info | SI (/content/early/2015/10/14/1508347112/suppl/DCSupplemental)
Metrics | Related Content (/content/early/2015/10/14/1508347112/?tab=related)
PDF (/content/early/2015/10/14/1508347112.full.pdf)
PDF + SI (/content/early/2015/10/14/1508347112.full.pdf?with-ds=yes)

Significance

Studies examining paternal exposure to diverse environmental stimuli propose that epigenetic marks in germ cells, including small noncoding RNAs such as microRNA (miR), transmit experience-dependent information from parent to offspring. However, these nongenetic mechanisms of transgenerational inheritance are poorly understood, specifically how these germ-cell marks may act postfertilization to enact long-term changes in offspring behavior or physiology. In this study, through zygote microinjection of nine specific sperm miRs previously identified in our paternal stress mouse model, we demonstrate that sperm miRs function to reduce maternal mRNA stores in early zygotes, ultimately reprogramming gene expression in the offspring hypothalamus and recapitulating the offspring stress dysregulation phenotype.

Abstract

Epigenetic signatures in germ cells, capable of both responding to the parental environment and shaping offspring neurodevelopment, are uniquely positioned to mediate transgenerational outcomes. However, molecular mechanisms by which these marks may communicate experience-dependent information across generations are currently unknown. In our model of chronic paternal stress, we previously identified nine microRNAs (miRs) that were increased in the sperm of stressed sires and associated with reduced hypothalamic–pituitary–adrenal (HPA) stress axis reactivity in offspring. In the current study, we rigorously examine the hypothesis that these sperm miRs function postfertilization to alter offspring stress responsivity and, using zygote microinjection of the nine specific miRs, demonstrated a remarkable recapitulation of the offspring stress dysregulation phenotype. Further, we associated long-term reprogramming of the hypothalamic transcriptome with HPA axis dysfunction, noting a marked decreased in the expression of extracellular matrix and collagen gene sets that may reflect an underlying change in blood–brain barrier permeability. We conclude by investigating the developmental impact of sperm miRs in early zygotes with single-cell amplification technology, identifying the targeted degradation of stored maternal mRNA transcripts including sirtuin 1 and ubiquitin protein ligase E3a, two genes with established function in chromatin remodeling, and this potent regulatory function of miRs postfertilization likely initiates a cascade of molecular events that eventually alters stress reactivity. Overall, these findings demonstrate a clear mechanistic role for sperm miRs in the transgenerational transmission of paternal lifetime experiences.

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry 56:3 (2015), pp 296–298 doi:10.1111/jcpp.12399

Commentary: We've only just begun: unravelling the underlying genetics of neurodevelopmental disorders – a commentary on Kiser et al. (2015)

David Coghill

UK

There is an interesting discussion on the potential role of impaired neurite outgrowth, synaptogenesis and synaptic plasticity. It makes good sense that, during early brain development, the genes impacting on these processes could play an important causal role. However, due to the very early onset of these disorders it is harder to see how impairments in plasticity, regulation of cell migration, neurite outgrowth and the establishment of effective circuits and network maturation (and in plasticity processes occurring later on in development) could be causal.

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

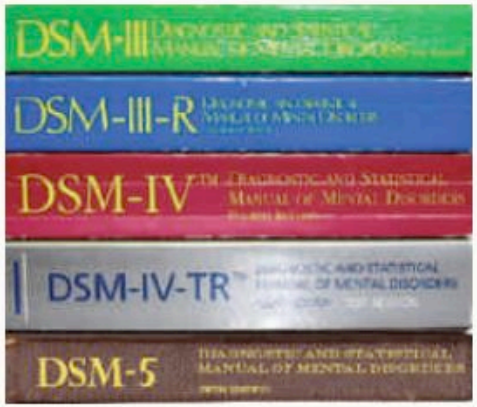
Journal of Child Psychology and Psychiatry 56:3 (2015), pp 228–247 doi:10.1111/jcpp.12328

Annual Research Review: Infant development, autism, and ADHD – early pathways to emerging disorders

Mark H. Johnson,[1] Teodora Gliga,[1] Emily Jones,[1] and Tony Charman[2]

[1]Centre for Brain and Cognitive Development, Birkbeck College, University of London; [2]Institute of Psychiatry, King's College London, London, UK

Background: Autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders, with a high degree of co-occurrence. **Methods:** Prospective longitudinal studies of infants who later meet criteria for ASD or ADHD offer the opportunity to determine whether the two disorders share developmental pathways. **Results:** Prospective studies of younger siblings of children with autism have revealed a range of infant behavioral and neural markers associated with later diagnosis of ASD. Research on infants with later ADHD is less developed, but emerging evidence reveals a number of relations between infant measures and later symptoms of inattention and hyperactivity. **Conclusions:** We review this literature, highlighting points of convergence and divergence in the early pathways to ASD and ADHD. **Keywords:** Neurodevelopmental disorder, prediction, risk factors, developmental pathways, ADHD, autism spectrum disorders.



EVOLVING DEFINITIONS

For just over a century, researchers have grappled with how to define autism — and what causes it.

1911
Swiss psychiatrist Eugen Bleuler coins the term 'autism' in describing self-absorbed adults with schizophrenia.

1943
US psychiatrist Leo Kanner publishes a report of 11 children with autism, defines disorder as "autistic disturbances of affective contact."

1944
Austrian paediatrician Hans Asperger publishes a report of children with profound social problems, lack of empathy and clumsiness.

1967
Bruno Bettelheim's *The Empty Fortress* claims that autism stems from social deprivation, adding fuel to the popular, though incorrect, theory that emotionally cold mothers were the cause.

Anni '70 - '80, i primi studi epidemiologici sui gemelli (Rutter M. 2000)

1980
'Infantile autism' is added to the Diagnostic and Statistical Manual of Mental Disorders (DSM) III. Defined by 6 criteria, including a lack of responsiveness to others, gross language and resistance to change.

1992
Asperger's syndrome becomes a distinct diagnosis when it's included in the tenth edition of the World Health Organization's diagnostic manual.

1994
The fourth edition of the DSM greatly expands the autism spectrum, outlining criteria for autistic disorder, Asperger's syndrome and pervasive developmenta disorder not otherwise specified (PDD-NOS).

2004, parte l'Autism Genome Project (AGP), il più ampio progetto di ricerca per l'identificazione di geni associati al rischio di autismo

2013
The fifth edition of the DSM is likely to merge th various autism disorders into a single category called autism spectrum disorder.

The Asperger's label has helped many who don't fit the classic autism model or stereotype to get a diagnosis and accept their autism.

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

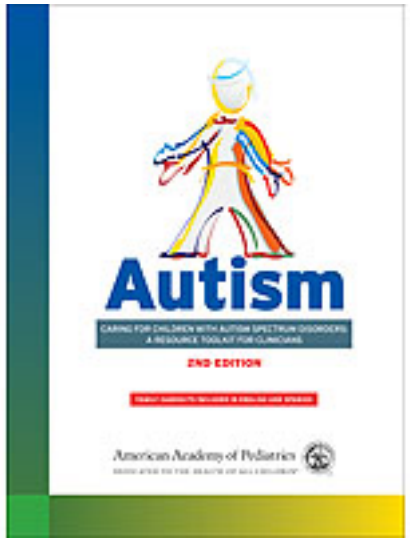
Identification and Evaluation of Children With Autism Spectrum Disorders

Chris Plauché Johnson and Scott M. Myers

Pediatrics 2007;120;1183; originally published online October 29, 2007;
DOI: 10.1542/peds.2007-2361

2nd edition (2013)

Autism: Caring for Children with Autism Spectrum Disorders: A Resource Toolkit for Clinicians



AUTISM SPEAKS™

100 Day Kit

A tool kit to assist families in getting the critical information they need in the first 100 days after an autism diagnosis.

Why does my child need a diagnosis of Autism?

There are however, several reasons having a diagnosis is important for your child. A thorough and detailed diagnosis provides important information about your child's behavior and development. It can help create a road map for treatment, by identifying your child's specific strengths and challenges and providing useful information about which needs and skills should be targeted for effective intervention. A diagnosis is often required to access autism specific services through early intervention programs or your local school district.

AUTISM SPEAKS™

100 Day Kit

A tool kit to assist families in getting the critical information they need in the first 100 days after an autism diagnosis.

HOW IS AUTISM DIAGNOSED?

Presently, there is not a medical test for autism; a diagnosis is based on observed behavior and educational and psychological testing. As the symptoms of autism vary, so do the routes to obtaining a diagnosis. You may have raised questions with your pediatrician. Some children are identified as having developmental delays before obtaining a diagnosis of autism and may already receive some **Early Intervention** or **Special Education services**. Unfortunately, parents' concerns are sometimes not taken seriously by their doctor and as a result, a diagnosis is delayed. *Autism Speaks* and other autism related organizations are working hard to educate parents and physicians, so that children with autism are identified as early as possible.

From birth to at least 36 months of age, every child should be screened for developmental milestones during routine visits. The American Academy of Pediatrics recommends that all children be screened for autism at their 18- and 24-month well-baby check-ups. If concerns about a child's development are raised, his or her doctor should refer the child to Early Intervention and a specialist for a developmental evaluation. Hearing and lead exposure screenings should be performed and an autism-specific screening tool, such as the **Modified Checklist of Autism in Toddlers (MCHAT),** should be used. (http://www.dbpeds.org/media/mchat.pdf)

National Autism Plan for Children (NAPC)

NAS, 2003

Plan for the identification, assessment, diagnosis and access to early interventions for pre-school and primary school aged children with autism spectrum disorders (ASD)

- On the basis of current evidence, primary screening for autism and ASD by the use of tests applied to the whole population at specific ages cannot be recommended. However, qualitative abnormalities suggestive of the core behaviours of ASD can be detected in pre-school and school age children. Parents or trained professionals can identify ASD if they have an awareness of normal development and the specific developmental impairments identified in research studies in autism and incorporated into checklists such as CHAT.

- The concept of child health surveillance as practised in primary care/child health services in the UK is a process of continuous dialogue between parents and health professionals (initially in the early pre-school period) that mutually informs about the development of a particular child. The aim is early and prompt identification of any developmental problem. Currently, (*Health for all children*, 4th edition, 2003) no routine tests of development are recommended in the pre-school years.

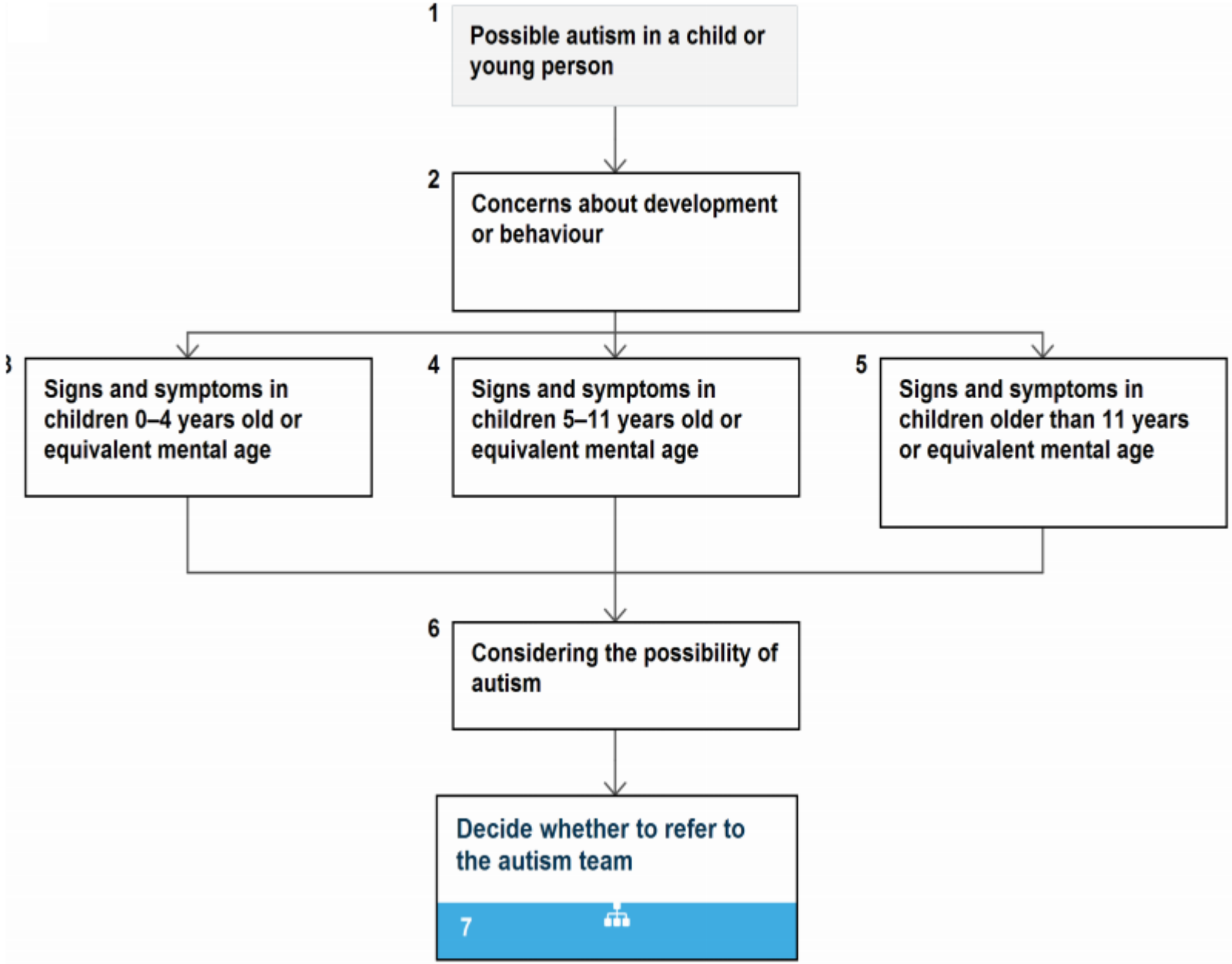
Quick Reference Guide, 2011
Autism
Recognition, refferral and diagnosis of children and young people on the autism spectrum

NHS
National Institute for Health and Clinical Excellence

Service organisation

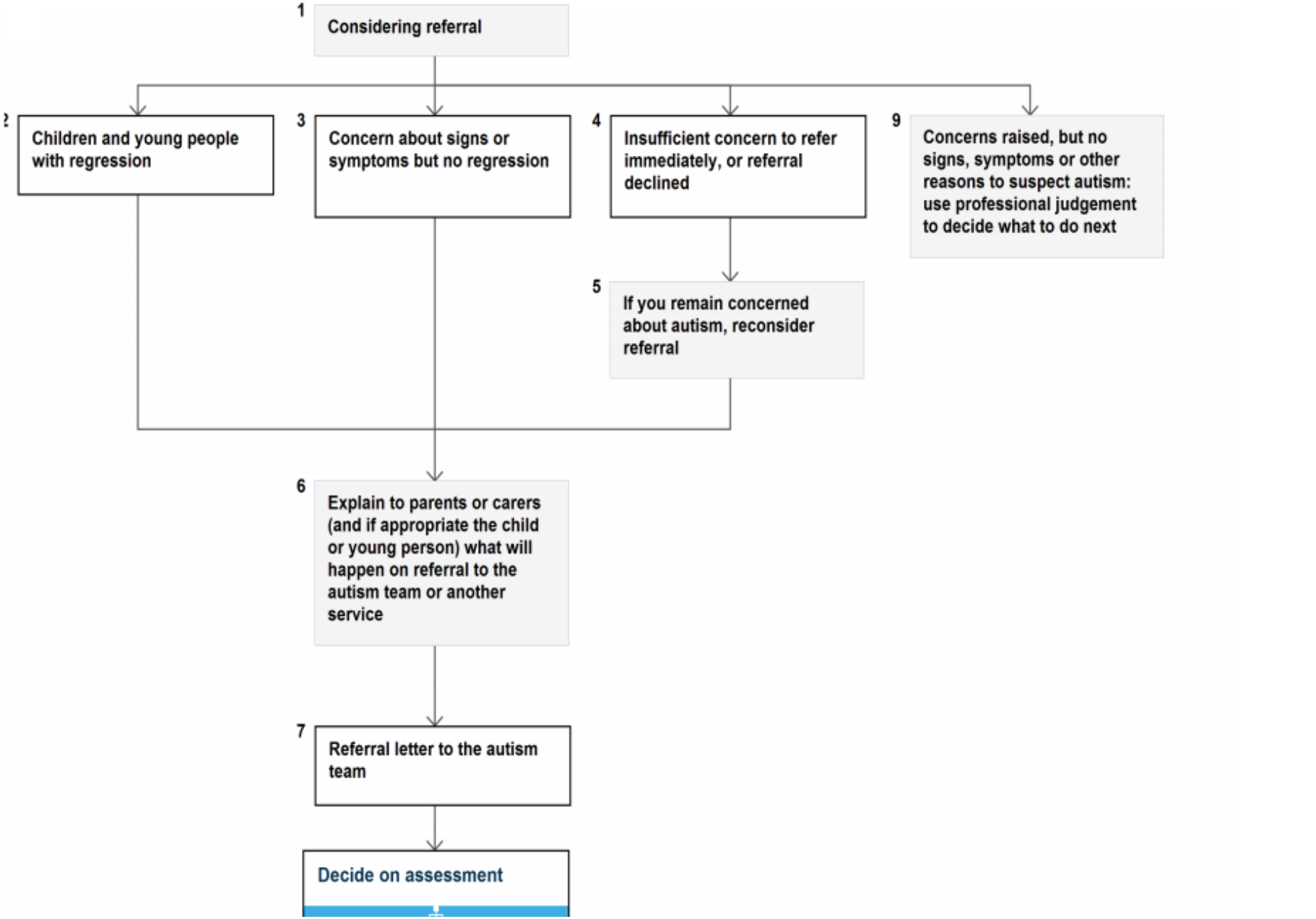
Strategy group

- A local autism multi-agency strategy group should be set up, with managerial, commissioner and clinical representation from:
  - child health and mental health services
  - education
  - social care
  - parent and carer service users
  - the voluntary sector.
- The local autism strategy group should appoint a lead professional to be responsible for the local autism pathway for recognition, referral and diagnosis of children and young people. The aims of the group should include:
  - improving early recognition of autism by raising awareness of the signs and symptoms of autism through multi-agency training (see tables 1–3 on pages 14–19)
  - making sure the relevant professionals are aware of the local autism pathway and how to access diagnostic services
  - supporting the smooth transition to adult services for young people
  - ensuring data collection and audit of the pathway takes place.


1
Possible autism in a child or young person
2
Concerns about development or behaviour
3
Signs and symptoms in children 0–4 years old or equivalent mental age
4
Signs and symptoms in children 5–11 years old or equivalent mental age
5
Signs and symptoms in children older than 11 years or equivalent mental age
6
Considering the possibility of autism
Decide whether to refer to the autism team
7

Referral of children and young people with possible autism

NICE *Pathways*



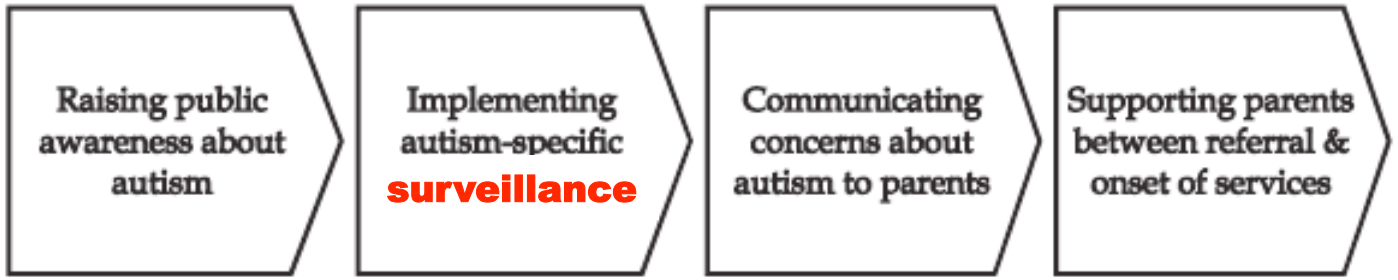


Figure 1. A sequence of four connected activities aimed at improving early identification of ASD and promoting successful referrals for Early Intervention services.

EARLY INTERVENTION

Presidenza del Consiglio dei Ministri

CONFERENZA UNIFICATA

OBIETTIVI ED AZIONI[1]

Accordo, ai sensi dell'articolo 9, comma 2, lettera c), del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e di Bolzano, le Province, i Comuni e le Comunità montane sulle "Linee di indirizzo per la promozione ed il miglioramento della qualità e dell'appropriatezza degli interventi assistenziali nel settore dei Disturbi pervasivi dello sviluppo (DPS), con particolare riferimento ai disturbi dello spettro autistico".

Rep. Atti n. 132/CU del 22/11/2012

2) Promuovere interventi mirati alla creazione di una rete assistenziale regionale integrata (R. MIUR)

a. Rilievo precoce, sostenuto da adeguata formazione, del sospetto di Autismo entro i primi due anni di vita (ad eccezione della Sindrome di Asperger ed alcuni casi di DPS-NAS) da parte del Pediatra di Libera Scelta ed invio tempestivo alle équipe specialistiche per i DPS dei Servizi di neuropsichiatria dell'Età Evolutiva.

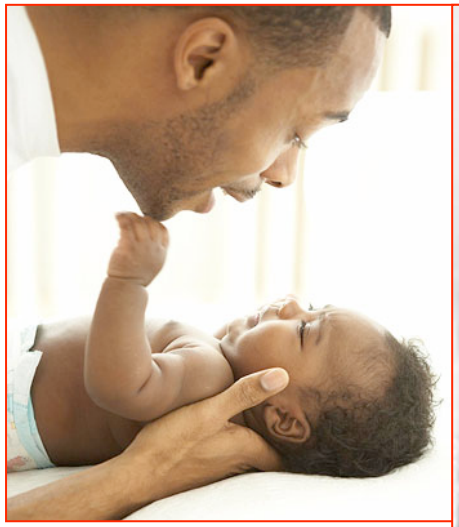
b. Razionalizzazione dei percorsi diagnostico-terapeutici secondo un modello di rete clinica e di approccio multiprofessionale, interdisciplinare ed età specifico per la diagnosi e la valutazione funzionale strutturata, e definizione di percorsi condivisi tra figure sanitarie, operatori sociali, insegnanti ed educatori per la costruzione e conduzione del progetto abilitativo individualizzato.

Quaderni acp 2012; 19(4): 169-176

Valutazione neuroevolutiva e promozione dello sviluppo psicomotorio 0-3 anni

Documento di consenso

A cura del Gruppo di lavoro multidisciplinare ACP, AIFI, FIMP, IOPTP, SIF, SINPIA, SIP, promosso da OMS, Ufficio Europeo e da EPA/UNEPSA: Giorgio Tamburlini* e Gherardo Rapisardi** (coordinatori), Adrienne Davidson***, Monica Pierattelli****, Marina Picca°, Donella Prosperi°°, Federica Zanetto°°° e con la collaborazione di Andrea Guzzetta°°°°



Quaderni acp 2013; 20(5): 219-220

salute **mentale**

Rubrica a cura di Angelo Spataro

CHAT o M-CHAT per l'individuazione dei bambini a rischio di autismo?

Intervista di Massimo Soldateschi* a Filippo Muratori**
*Pediatra di famiglia, ACP Toscana, Gruppo "Salute Mentale" dell'ACP; **Dipartimento di Neuroscienze dell'Età Evolutiva, IRCCS Stella Maris, Università di Pisa

L'intervento precoce può modificare l'evoluzione del quadro sintomatologico del bambino affetto da autismo. Esistono a uso del pediatra due strumenti di screening per l'autismo maggiormente studiati in termini di ricerca scientifica: la CHAT e la M-CHAT (o CHAT modificata). Quali dei due strumenti offre maggiori possibilità di riconoscere una condizione di rischio di autismo senza incorrere in troppi falsi negativi e/o falsi positivi?

Journal of Autism and Developmental Disorders
December 2013, Volume 43, Issue 12, pp 2844-2854
Children's Compliance with American Academy of Pediatrics' Well-Child Care Visit Guidelines and the Early Detection of Autism
Amy M. Daniels, David S. Mandell

Current Opinion in Pediatrics
February 2013, Volume 25, Issue 1, pp 130-143
doi: 10.1097/MOP.0b013e32835c2b70
Autism spectrum disorders: a pediatric overview and update
Tchaconas, Alexisa; Adesman, Andrewb
OFFICE PEDIATRICS: Edited by Henry H. Bernstein

Daniels A., Mandell, D., S. (2013). Children's Compliance with Autism Academy of Pediatrics' Well – Child Care Visit Guidelines and the Early Detection of Autism.

Journal of Autism Developmental Disorder, 43: 2844- 2854.

http://rd.springer.com/article/10.1007/s10803-013-1831-x

J Autism Dev Disord (2013) 43:2844–2854
DOI 10.1007/s10803-013-1831-x

ORIGINAL PAPER

Children's Compliance with American Academy of Pediatrics' Well-Child Care Visit Guidelines and the Early Detection of Autism

Amy M. Daniels · David S. Mandell

Published online: 26 April 2013

Abstract This study estimated compliance with American Academy of Pediatrics (AAP) guidelines for well-child care and the association between compliance and age at diagnosis in a national sample of Medicaid-enrolled children with autism ($N = 1{,}475$). Mixed effects linear regression was used to assess the relationship between compliance and age at diagnosis. Mean age at diagnosis was 37.4 (SD 8.4) months, and mean compliance was 55 % (SD 33 %). Children whose care was compliant with AAP guidelines were diagnosed 1.6 months earlier than children who received no well-child care. Findings support that the timely receipt of well-child care may contribute to earlier detection. Additional research on the contribution of compliance, well-child visit components and provider characteristics on the timely diagnosis of autism is needed.

Keywords Compliance · Well-child care · Autism · Diagnosis · Medicaid

An earlier version of this article was presented as an abstract at the International Meeting for Autism Research in San Diego, CA in 2011.

Present Address:
A. M. Daniels (✉)
Autism Speaks, 1 East 33rd Street, 4th Floor, New York, NY 10016, USA
e-mail: amy.daniels@autismspeaks.org

A. M. Daniels
Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA

D. S. Mandell
Center for Mental Health Policy and Services Research, Perelman School of Medicine, University of Pennsylvania, 3535 Market Street, 3rd Fl., Philadelphia, PA 19104, USA

D. S. Mandell
Center for Autism Research, The Children's Hospital of Philadelphia, 3535 Market Street, 3rd Fl., Philadelphia, PA 19104, USA

Introduction

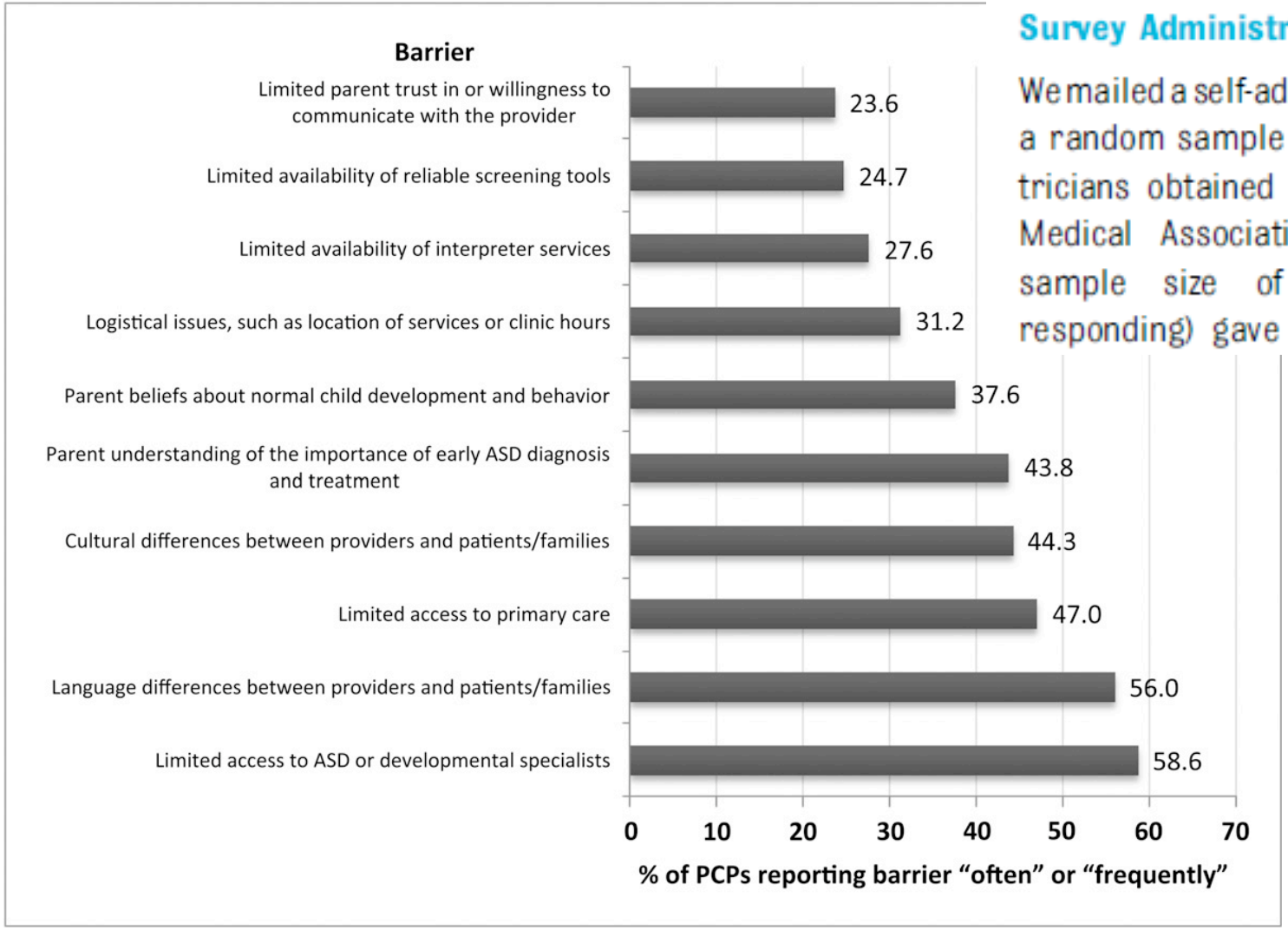
Early identification of autism is critical to optimizing outcomes. Studies consistently demonstrate that intensive early intervention improves cognition and reduces core symptoms of autism (Howlin 2008; Howlin et al. 2009; Ospina et al. 2008; Seida et al. 2009; Vismara and Rogers 2010). Despite research showing that clinicians can reliably diagnose autism starting when children are 2 years of age (Johnson et al. 2007; Johnson 2008), many children are not diagnosed until much later (Autism and Developmental Disabilities Monitoring Network (ADDM) Surveillance Year 2008 Principal Investigators and Centers for Disease Control and Prevention (DCD) 2012; Mandell et al. 2005; Mandell et al. 2010; Shattuck et al. 2009). A delay in diagnosis translates into a missed opportunity to provide crucial services to reduce the disorder's severity and improve quality of life.

In recent years many studies have examined factors associated with age at autism spectrum disorder (ASD) diagnosis (Fountain et al. 2011; Mandell et al. 2002, 2005, 2010; Ouellette-Kuntz et al. 2009; Perryman 2009; Rosenberg et al. 2011; Shattuck et al. 2009). In general, studies have found autistic disorder (AD) to be diagnosed earliest (Chakrabarti and Fombonne 2001; Fernell and Gillberg 2010; Goin-Kochel et al. 2006; Howlin and Asgharian 1999; Latif and Williams 2007; Mandell et al. 2010; Noterdaeme and Hutzelmeyer-Nickels 2010; Oslejskova et al. 2007; Rosenberg et al. 2011; Wiggins et al. 2006; Williams et al. 2008), and that age at diagnosis for all ASDs has decreased over time (Chamak et al. 2011; Keen and Ward 2004; Latif and Williams 2007; Lingam et al. 2003; Mandell et al. 2010;

Pediatrician Identification of Latino Children at Risk for Autism Spectrum Disorder

Katharine E. Zuckerman, Kimber Mattox, Karen Donelan, Oyundari Batbayar, Anita Baghaee and Christina Bethell

Pediatrics 2013;132;445; originally published online August 19, 2013;



Survey Administration

We mailed a self-administered survey to a random sample of California pediatricians obtained from the American Medical Association Masterfile.[19] A sample size of 500 (with 60% responding) gave adequate power to


Buon
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